

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 09/657446
Applicant : David Edgren
Filed : 2000-09-08
Art Unit : 1615
Examiner : Blessing M. Fubara
Docket No. : ARC 2762C1
Customer No. : 30766
Title : Extended Release Dosage Form

Confirmation No. 1540

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. 1.132

David E. Edgren declares as follows:

1. I am a joint inventor of the subject matter of the above-identified patent application.
2. I received a Bachelor of Science Degree in Chemistry at the University of California Santa Barbara in 1972.
3. I have been working in the field of controlled drug delivery at the ALZA Corporation for 31 year. I am an inventor on 47 United States Patents pertaining to this technology. I am co-author of the chapter on controlled drug delivery in Kirk-Othmer Encyclopedia of Chemical Technology Controlled Release Technology (Pharmaceuticals), Volume 7, p 274-300 (1993).
4. The drug used in Examples 1 and 2 of the Bartoo et al. reference (U.S. Patent No. 4743248) is the acidic drug cimetidine hydrochloride. The solution chemistry data of cimetidine hydrochloride is shown in Exhibit I. Cimetidine hydrochloride forms a saturated aqueous solution at a concentration of 290 mg/ml at 37°C and has an osmotic pressure of 32 atm at 37°C.
5. For the experiments, a sorbitol solution that would be isotonic with a saturated solution of cimetidine hydrochloride was prepared by dissolving 122 g sorbitol in de-ionized water made to 500 ml. The sorbitol solution had a concentration of 244 mg/ml and an osmotic pressure of 32 atm at 37°C. The osmotic pressure of sorbitol as a function of concentration is shown in Exhibit II.

6. 300 mg \pm 10 mg of each of hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), hydroxypropylcellulose (HPC), cellulose acetate, and ethyl cellulose were added to 15 ml of artificial gastric fluid, USP 26/NF 21, pH = 1.3 (Media A), artificial intestinal fluid, USP 26/NF 21, pH = 7.3 (Media B), 244 mg/ml sorbitol solution prepared with de-ionized water, pH = 4.0 (Media C), and 244 mg/ml sorbitol solution prepared with Media B, pH 7.1 (Media D). After 24 hours at 37°C, samples were shaken a few times and then observed. Solubilities of HPMCP, HPMC, PEG, HPC, cellulose acetate, and ethyl cellulose in Media A-D are shown in Exhibit III.

7. As shown in Exhibit III, aqueous solubilities of HPMCP and PEG do not respond to osmotic pressure while aqueous solubility of HPC responds to osmotic pressure. PEG is soluble regardless of pH and osmotic pressure. HPMCP is insoluble at low pH and soluble at high pH regardless of osmotic pressure. HPC is soluble at low osmotic pressure and insoluble at high osmotic pressure regardless of pH.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: August 4, 2006

David E. Edgren
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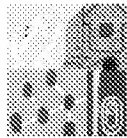
EXHIBIT I

Solution Chemistry Values for
Cimetidine HCl

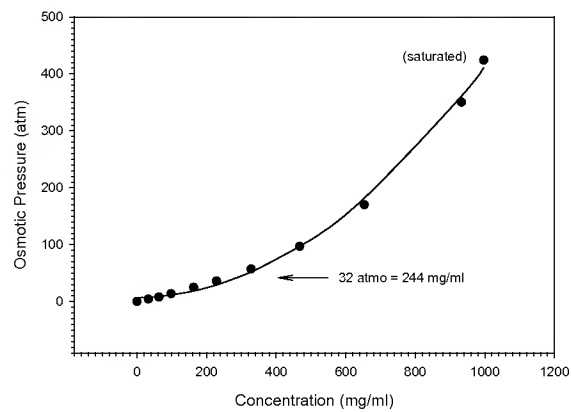
Drug	Molecular Weight (g/mole)	pH	Solubility at 37°C (mg/ml)	Osmotic Pressure at 37°C (atmospheres)
Cimetidine HCl	288.81	Acidic	290	32

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EXHIBIT II



Osmotic Pressure of Sorbitol vs Concentration



Notes:

- 1) Temperature: 37°C
- 2) Curve Fit: $\pi = 7.212 + 0.0039 C + 0.0004 C^2$ ($r^2 = 0.9972$)
- 3) NB 1525.099, 3435.113-117, 6377.049&107



EXHIBIT III

Solubility of Excipients of Inner Wall
At Low and High pH and at Low and High Osmotic Pressure

Inner Membrane	Excipient	Media A pH < 5, 6 atm,	Media B pH >5, 4 atm	Media C pH < 5, 32 atm	Media D pH > 5, 36 atm
Example in Bartoo et al	Cellulose acetate	insoluble	insoluble	insoluble	insoluble
	HPMCP	insoluble	soluble	insoluble	soluble
	PEG	soluble	soluble	soluble	soluble
Example in Instant Application	Ethyl cellulose	insoluble	insoluble	insoluble	insoluble
	HPC	soluble	soluble	insoluble	insoluble